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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,434	05/07/2002	Elizabeth Tournier-Lasserve	03715.0102	4231

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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 07/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,434	TOURNIER-LASSERVE ET AL.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2004 and 02 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8-16,19-23,25 and 26* is/are pending in the application.

4a) Of the above claim(s) *1 and 19-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-16,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/14/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 8-16 and 25) in the reply filed on December 27, 2004 is acknowledged. The traversal is on the ground(s) that the restriction is improper since Serebriiskii et al. do not teach or suggest isolated nucleic acid sequences comprising SEQ ID NO: 1-28 for detecting Krit1 protein mutations. This is not found persuasive because Serebriiskii et al. teach cloning of the Krit1 protein (page 1044, paragraphs 3-5), therefore, they expressly teach its nucleic acid sequence. Since claim 1 is drawn to a nucleic acid sequence comprising SEQ ID NO: 1, for example, which is a primer to amplify Krit1, Serebriiskii et al. inherently teach SEQ ID NO: 1.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1 and 19-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 27, 2004.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

4. Claims 8-16, 25 and 26 will be examined.

Request for Information Under 37 C.F.R. § 1.105

5. The request for information was mailed to Applicants on March 7, 2005 and the reply was received August 2, 2005. Applicants' response is accepted as mostly satisfactory, because of the following statement: "Applicants submit that there was no indication concerning the gene Kritl in the poster, because the Kritl gene had not been identified as of May, 1998." However, the next to the last sentence of the poster abstracts states the following: "Mapping on a YAC contig and fine characterization of the transcriptional units located within the CCM1 interval allowed identification of 4 known genes (CDK1, PAS1, HUMLD14 and KRIT1) and 24 transcriptional units with no known sequence homology." (emphasis added). Therefore, contrary to Applicants' statement, KRIT1 is specifically mentioned in the poster abstract.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 8-16, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or

guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 8-16, 25 and 26 are broadly drawn to a method of diagnosing cavernomas in an individual by detecting a presence of a mutation in a Krit1 gene in a sample obtained from the individual. However, as will be further discussed, there is no support in the specification and prior art for the method. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Working Examples

The specification has one working example, in which 20 CCM patients from families exhibiting cavernomas were examined for mutations in the Krit1 gene (pages 14 and 15). As shown in the specification, only eight of those patients exhibited mutations in the Krit1 gene (page 5, lines 14-30), whereas 12 of those patients did not exhibit any mutations (page 7, lines 24-35). Applicants concluded with the following statemet (page 7, lines 35-38):

"Finally, some of these families, although showing a high probability of being linked to the CCM1 locus, may, in fact, be linked to one of the other CCM loci."

Guidance in the Specification.

The specification provides no evidence that the detection of mutations in the Krit1 gene would automatically result in the detection of cavernomas. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses that 8 out of 20 patients from families afflicted with CCM had Krit1 mutations, without specifying how many

of these patients exhibited CCM lesions. Moreover, a thorough review of the prior art fails to show any enabled teachings of a one-to-one correlation between the presence of cavernomas in an individual and presence of Krit1 mutations.

The unpredictability of the art and the state of the prior art

The specification discloses that 8 of 20 patients from families affected with CCM exhibited mutations in the Krit1 gene when their genomic DNA was analyzed. However, there is no evidence that the presence of mutations was correlated with the presence of CCM lesions. There is a great deal of unpredictability in the correlation (or lack of it) between the presence of cavernomas and mutations in the Krit1 gene in affected individuals.

First, as indicated by Bergametti et al. (Am. J. Hum. Genet., vol. 76, pp. 42-51, 2005), only 40% of families with CCM have been linked to the CCM1 locus, which was found to contain the Krit1-encoding DNA (page 42, last paragraph). Then the presence of cavernomas does not correlate with the Krit1 mutations even in families linked to the CCM1 locus, as evidenced by Cave-Riant et al. (Eur. J. Hum. Genet., vol. 10, pp. 733-740, 2002), who examined genomic DNA from 121 individuals who either had an affected family member and/or had multiple cavernomas (page 734, fourth paragraph). Of these 121 individuals, 52 were found to have mutations in the Krit1 gene (page 734, last paragraph; page 735, first and second paragraph). As there is no indication in the reference of how many of these 121 individuals had cavernomas, it is not possible to ascertain what is the relationship between the presence of the cavernomas and the Krit1 mutations.

A clear example of the fact that the presence of Krit1 mutations does not mean that an individual has cavernomas was provided by Lucas et al. (BMC Neurology, vol. 3, pp. 1-6, 2003), who investigated occurrence of CCMs in three-generational family harboring a frameshift mutation

in the Krit1 gene (Abstract; page 2, paragraphs 5-8). They found that one sibling which had the mutation showed no CCMs on the MRI (page 3, last paragraph). The authors conclude with the following statement (page 5, fourth paragraph):

"Nonetheless, the variable clinical and radiological traits in affected individuals of the same family exclude a direct correlation between clinical expression and genotype. The affected siblings, in addition to the Y634X mutated phenotype, share the same paternal chromosome, so a variable genetic background, at least in the vicinity of CCM1, can be excluded."

Finally, Reich et al. (Neurology, vol. 60, pp. 1135-1138, 2003) examined a correlation between sporadic cerebral cavernomas and Krit1 mutations in the cells from cavernomas and adjacent normal brain tissue of 72 patients (Abstract; page 1136, paragraphs 2-6; pag3 1137, first paragraph), and found no mutations in the Krit1 gene (page 1137, second and third paragraphs).

In conclusion, the presence of cavernomas in a patient does not exhibit a correlation to the presence of mutations in the Krit1 gene.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply method to diagnosis of cavernomas. The Krit1 gene encodes 19 exons and 16 introns, and so far most of the sequence has not been examined for the presence of all possible mutations. Even with the mutations already detected, it is not clear to what degree each one of them separately contributes (if at all) to the development of cavernomas in individuals harboring the mutation. Therefore, one would have to perform a study in which all of the possible Krit1 mutations would have to be determined and correlated either individually or as haplotypes with the presence of cavernomas. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the presence of Krit1 mutations does not always result in the presence of cavernomas and the presence of cavernomas is not associated with the presence of Krit1 mutations, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the use of the mutations in a single gene for diagnosis of cavernomas as broadly claimed. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

8. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
Art Unit 1637

Teresa Strzelecka
7/19/06